SELF-CONTROL AND INHIBITION IN THE ADRENAL GLAND.

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THE secretory activity of the adrenal gland is under the control of the sympathetic nervous system: stimulation of the splanchnic nerves induces a secretion of adrenalin. Since adrenalin itself stimulates sympathetic nerve-endings, it would follow that the injection of adrenalin itself should elicit a further secretion of adrenalin from the gland. It would appear therefore that if once a sufficiently massive secretion of adrenalin had been induced, the activity of the gland should continue to stimulate itself to further activity until it is exhausted, a short stimulation of the gland initiating a kind of avalanche phenomenon. We know that this is not so, since the effect of an injection of adrenalin passes off with extreme rapidity. There must exist, therefore, a controlling mechanism which protects the gland against such self-stimulation. This mechanism is disclosed by a study of the appearance of the gland, by means of the osmic vapour method, after an injection of adrenalin.

Before discussing the effect produced in this way we must briefly recall the appearance of the normal resting gland of a mouse as shown by this method and described in a previous paper (Cramer, 1919). It may be added that in all our observations the whole gland has been cut in serial sections, so that it is possible to make a comparison between corresponding parts of different glands. This precaution is essential. The following descriptions refer to appearances in section through the control part of the medulla, either along its short or its long axis, but nearer that pole from which the central vein eventually emerges. The appearance of the normal gland is illustrated in Fig. 1. The medulla is large in relation to the cortex. The bulk of the latter is made up of columns of cells of the zona fasciculata, while the innermost zone—the zona reticularis—surrounds the medulla as a sharply defined continuous, even, narrow band. The lipoid globules are situated mainly in the cells of the outer two-thirds of the cortex. When as a result of exposure to cold or of an injection of β-tetrahydronaphthylamin the gland is actively

secreting adrenalin, the secretion begins and is most massive in the cells situated in the centre of the medulla around the central vein and its tributaries. At the same time the cortex shows signs of activity by a spreading of the lipoid globules from the periphery towards the central parts, so that they are distributed over the whole cortex. As has been pointed out in a previous paper (Cramer, 1919), the secretion of adrenalin by the medulla stimulates at once the formation of new adrenalin, and in this the innermost part of the cortex appears to play an important part. For if active secretion is prolonged, globules of materials having the same staining reaction as adrenalin appear in the innermost part of the cortex in the cells of the zona reticularis, which, like the active medulla, shows congestion. The occurrence of adrenalin—or a precursor—in the innermost part of the cortex has been confirmed by Hartman (1923). The point of importance in connection with the following observations is that the cortex participates in the activity of the medulla, and that there is a particularly intimate close functional relationship between the medulla and the immediately adjacent cells of the cortex in the zona reticularis.

After an injection of adrenalin, the peripheral cells of the medulla—those immediately adjacent to the cortex—lose their adrenalin (see Fig. 2). They thereby lose the typical appearance of medullary cells, and may be mistaken for cells of the cortex. At first sight this gives the impression as if the zona reticularis had hypertrophied enormously at the expense of the medulla, which appears much smaller than in the normal animal. It is obvious that in the few minutes which have elapsed since the injection of adrenalin no such hypertrophy can possibly have taken place, and closer inspection reveals in this broad zone islets of typical medullary cells still filled with granules of adrenalin. Fig. 3 gives a high-power view of this zone. In some parts these groups of cells are still connected with the medulla and project like peninsulas into this zone. This broad zone therefore belongs to the medulla, and is composed of medullary cells which have lost their content of adrenalin in varying degrees. An adrenalin-free zone of the medulla has thus been interposed between the cells of the zona reticularis of the cortex and the adrenalin-containing cells of the medulla as the result of the injection of adrenalin. The formation of such a zone is interpreted as interfering with the interaction of cortex and medulla, which is essential for the normal functional activity of the gland. It is the morphological manifestation of the check which the gland imposes upon itself in this condition, and by which it protects itself against self-exhaustion. We propose to call this phenomenon "self control" of the adrenal.

The same phenomenon has been observed in another condition, namely, after thyroid feeding over a prolonged period. It was, in fact, first observed several years ago in mice fed with small doses of thyroid over three months, and was then recorded in the accompanying drawings (Fig. 4). The adrenalin-free peripheral zone, with occasional islets of cells containing sparse granules of adrenalin, is particularly distinct in this condition. It was possible to demonstrate conclusively that this zone belonged to the medulla, and not to the cortex, by discontinuing the thyroid feeding and noticing the behaviour of this zone during the recovery. Fig. 5 is taken from the adrenal of such an animal when after $3\frac{1}{2}$ months of thyroid feeding the administration of thyroid

had been discontinued for three days, and shows the gradual reappearance of adrenalin granules in the cells of this zone. The gland still shows the broad zone of adrenalin-free medullary cells, but the islets of cells containing adrenalin have become much more numerous. Fig. 6 gives a high-power view of this zone, showing here and there cells or cell-groups renewing their load of adrenalin. In some of these cell-groups the granules of adrenalin are exceptionally large.

At the time when these observations on thyroid-fed animals were first made the significance of this process was not clearly understood. Its occurrence after injection of adrenalin has enabled us to interpret it, as stated above, as a mechanism of " self-control " of the gland.

In many of the thyroid-fed animals the cortex also exhibits a change in the distribution of the lipoid globules. Instead of being situated mainly in the outer half or two-thirds of the cortex—that is, the zona glomerulosa and the outer half of the zona fasciculata, as they do in the normal resting gland—they remain in the cells of the zona glomerulosa but disappear from the outer part of the zona fasciculata. Sometimes the innermost cells of the zona fasciculata are filled with these globules, so that a narrow band of lipoid-containing cells surrounds the medulla. But in other cases there is an extensive disappearance of the lipoid from the cortex, except, as already stated, the narrow peripheral zone of the cells of the zona glomerulosa. This cortical change frequently accompanies the medullary change described above as " self-control," but does not always do so and therefore has a different significance. The key to its interpretation is furnished by the following observations, which show that it is the outstanding feature of the change induced in animals exposed to heat. As will be shown, it represents an inhibition of the functional activity of the gland.

It is necessary to recall here briefly the conception which we have developed in previous papers of the thyroid-adrenal apparatus as a factor in the heat-regulation of the body (Cramer 1916, 1918, 1919, 1920 and 1924). We showed that the active secretion of the hormones of these two glands increases heat-production. Adrenalin by its peripheral vaso-constriction also diminishes heat-loss. It is clear, therefore, that these two hormones affect both the physical and the chemical heat-regulation of the body. Exposure to cold, which calls for increased heat-production and diminished heat-loss, is a powerful stimulus to the functional activity of these glands. Conversely, prolonged functional activity of these glands not due to stimulation by a cold environment produces fever accompanied by rigor. This conception has been confirmed by the work of Boothby and Sandiford (1923), who measured the calorigenic action of adrenalin, by Hartman (1923) and by Cannon, who both confirmed by different methods that cold is a powerful stimulus to the adrenal gland. It is clear that the regulation of the body-temperature through increased functional activity of the thyroid-adrenal apparatus can only be efficient in one direction—namely, in the direction of maintaining the body-temperature at a higher level than that of the surrounding environment. If, now, an animal such as the mouse or the rat, which have no sweat-glands andc annot increase heat-loss through perspiration, is placed in a warm environment having a temperature approaching that of the animal itself, regulation by heat-loss is eliminated. Then even a slight

activity of the thyroid-adrenal apparatus would, by increasing heat-production, necessarily lead to a hyperpyrexia and endanger the life of the animal. It would, in fact, produce heatstroke. Experimentally this condition can be reproduced by the injection of β-tetrahydronaphthylamin into animals kept in different thermal environments. We have shown in a previous paper (1920) that a slight stimulation of the thyroid-adrenal apparatus by the injection of a dose of β-tetrahydronaphthylamin, so small that it produces not even a rise in temperature if the animal is kept in a cool environment, will produce hyperpyrexial heatstroke if the animals are kept in a moderately warm room, or even if several animals are crowded together in a small cage. If in a hot environment adrenal activity is likely to endanger the life of the organism, we may expect that the organism will react to exposure to heat by an inhibition of the adrenal gland.

Mice are very sensitive to heat. It is possible to keep mice alive for weeks at a temperature of 37°–38° C. The animals remain quite well. But even a slight increase in the temperature beyond 38° C. will kill them, although the external temperature may only be one or two degrees Centigrade above their body temperature. When one examines the adrenals of mice kept for several days at 37°–38° C. by the osmic vapour method the medulla frequently shows no obvious change. The cells are fully loaded with adrenalin granules. Some animals may show the phenomenon of " self-control " just described in which adrenalin disappears from the peripheral cells of the medulla. This change, however, is not always present. But the cortex always shows a distinct change, namely an extensive disappearance of the lipoid globules. These disappear completely from the zona fasciculata in which they are normally present, and only a narrow band of lipoid-containing cells remains in the outermost layer of the zona glomerulosa. At the same time the animals are in an excellent condition of nutrition and show abundant adipose tissue. The glandular adipose tissue in which the adrenal lies embedded is filled with ordinary fat, with the result that the normal brown colour has disappeared and it looks yellow, like ordinary adipose tissue. The disappearance of lipoid from the cortex is therefore in striking contrast to the condition in the other deposits of adipose tissue. The statement made above that the adrenals of mice exposed to heat show sometimes very distinctly the phenomenon of " self-control "—disappearance of adrenalin from the periphery of the medulla—is illustrated in Fig. 7. In such cases there is also a disappearance of lipoid from the cortex, but this is not as complete as in animals in which the medulla has retained its normal load.

It is known that the presence of lipoid in the cortex is absolutely independent of the nutrition of the animal. For even in complete emaciation the cortex has its normal load of lipoid. The fact that in starvation the cortex retains so tenaciously its lipoid when the insistent demand exhausts all the other deposits of fatty material gives a special significance to the disappearance of lipoid as a result of exposure to heat. Such a complete disappearance of lipoid has been observed so far only in severe pathological conditions leading to the death of the organism—for instance in many severe bacterial infections.

It will be recalled that activity of the gland, such as can be produced, for instance, by exposure to cold, is associated with a spreading of the lipoid from the outer half over the whole cortex—a migration from the periphery of the

cortex towards the medulla. Exposure to heat produces a disappearance of the cortical lipoid. We conclude, therefore, that *activity of the gland is accompanied by a spreading of the cortical lipoid over the whole cortex, inhibition of the gland by a disappearance of the cortical lipoid.*

SELF-CONTROL AND INHIBITION IN PATHOLOGICAL CONDITIONS.

The existence of these two mechanisms of "self-control" and "inhibition" throws light on some pathological problems of the adrenal. Since the mechanism of "self-control" comes into action by thyroid feeding, *i. e.* in experimental hyperthyroidism, it is likely that the condition of this mechanism may play an important part in clinical hyperthyroidism. Inefficiency of this mechanism may be as important an ætiological factor in Graves's disease as the degree of hyperfunction of the thyroid. A degree of thyroid hyperactivity which in a normal organism may produce a condition remaining within physiological limits owing to the efficiency of the mechanism of self-control in the adrenal, will produce a greatly exaggerated effect if this mechanism is not efficient. From this point of view the functional condition of the suprarenal may be an important factor in the ætiology of Graves's disease. The suggestion that the adrenals become involved in Graves's disease has also been made on clinical grounds by Langdon Brown (1923). He points out that the disordered function of the adrenals may become the predominant factor in the course of the disease, and may carry it on, so to speak, even when the hyperactivity of the thyroid gland has subsided. It is not suggested here that this occurs in every case of the disease. It is well known that different cases of Graves's disease react very differently to similar treatment—a fact which suggests differences in the underlying condition in different cases. There is also the curiously paradoxical fact that in some cases of Graves's disease adrenalin given repeatedly by the mouth greatly relieves the condition. The effect is puzzling, and contrary to all *à priori* expectation. The demonstration of the mechanism of self-control in the adrenal which can be brought into action by adrenalin offers the solution of this therapeutic puzzle. The same explanation may perhaps apply to the beneficial effects which have been obtained quite recently by the oral administration of iodine (Plummer 1923, Starr 1924, Fraser 1925). This produces in many cases a remission which is as abrupt and as extensive as that following subtotal thyroidectomy. The effect is, however, not permanent, and the disease cannot be cured in this way. If the administration of iodine is stopped, the metabolic rate rises again rapidly and the symptoms reappear in a few weeks. It is interesting to note that this therapeutic puzzle was discovered as a result of a mistake in 1863 by Trousseau, who, by a lapse of the pen, prescribed to a patient suffering from Graves's disease tincture of iodine instead of tincture of digitalis.

The disappearance of the cortical lipoid in response to physiological conditions imposing an inhibition on the activity of the gland gives a clue to the interpretation of this phenomenon under pathological conditions. As already stated, in human post-mortem material it has been observed frequently though not constantly in many virulent bacterial infections. In a previous paper

(Cramer 1919) we have recorded it as a terminal stage in such experimental infections as gas gangrene, streptococcal septicæmia and diphtheria. In these conditions there is in addition a depletion of the load of adrenalin from the adrenal medulla. In a separate paper we intend to record observations on the intermediate stages of bacterial infections, which show that many bacterial toxins stimulate the activity of the gland. Only if the infection is of sufficient virulence does the inhibitory effect manifest itself on the cortex, thus preventing it from carrying out its normal function of assisting the active medulla in recharging itself with adrenalin. The relation of the gland to bacterial infections will be discussed more fully in that paper.

SUMMARY.

The adrenal gland possesses the power to control its functional activity in such a way as to prevent the gland from stimulating itself to complete exhaustion. The existence of such a mechanism is necessitated by the fact that the gland is stimulated to secretion by the sympathetic, and secretes as its specific hormone a substance—adrenalin—which itself specifically stimulates the sympathetic. It is shown that the injection of adrenalin and also prolonged feeding with thyroid gland produce characteristic changes in the adrenal medulla, which effect a "self-control" of the gland.

In addition there is a mechanism which effects an "inhibition" of the functional activity of the gland. This mechanism is located in the cortex and manifests itself as a disappearance of the cortical lipoid. It can be most readily demonstrated by exposing an animal to conditions such as a hot environment under which an activity of the gland would lead to the death of the animal by heatstroke.

The bearing of these conceptions on the pathology of the adrenal and thyroid is briefly discussed.

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DESCRIPTION OF PLATES.

FIG. 1.—Adrenal of normal mouse. × 60. (Reprinted, by permission, from the *Sixth Scientific Report of the Imperial Cancer Research Fund.*) The lipoid granules have been dissolved out by the Canada balsam, and are represented by vacuoles. Note the sharp and continuous divisions between medulla and cortex.

FIG. 2.—Adrenal of mouse 20 minutes after injection of 0·015 mgm. adrenalin. × 66. Shows appearance of adrenalin from peripheral parts of the medulla—"self-control." The right-hand side of the dotted square still lies inside the medulla.

FIG. 3.—Same animal. High-power view of the area enclosed in dotted square shown in Fig. 2. × 740.

FIG. 4.—Adrenal of mouse fed for 3 months with small doses of thyroid gland. × 75. Shows essentially the same change as found after adrenalin. Gland has been cut through its short axis.

FIG. 5.—Adrenal of mouse fed for 3 months with small doses of thyroid gland. Thyroid feeding discontinued 3 days before mouse was killed. × 75. Appearance similar to that in Fig. 4, but numerous islets of adrenalin containing cells are beginning to appear in the peripheral part of the medulla, of which the bulk is still free from adrenalin. Gland cut along its long axis.

FIG. 6.—Same animal. High-power view of the area in the peripheral part of the medulla outlined in Fig. 5. × 460. Shows the gradual reappearance of adrenalin in isolated cells and groups of cells. There is a great difference in the size of the adrenalin granules, some of which are very coarse.

FIG. 7.—Atypical effect of heat. Adrenal of mouse kept for 2 days at 37° C. × 75. The medulla shows a disappearance of adrenalin from the peripheral parts similar to the change observed after adrenalin and thyroid feeding. There is also a patchy disappearance of the lipoid from the cortex, indicated in the figure by differences in shading.

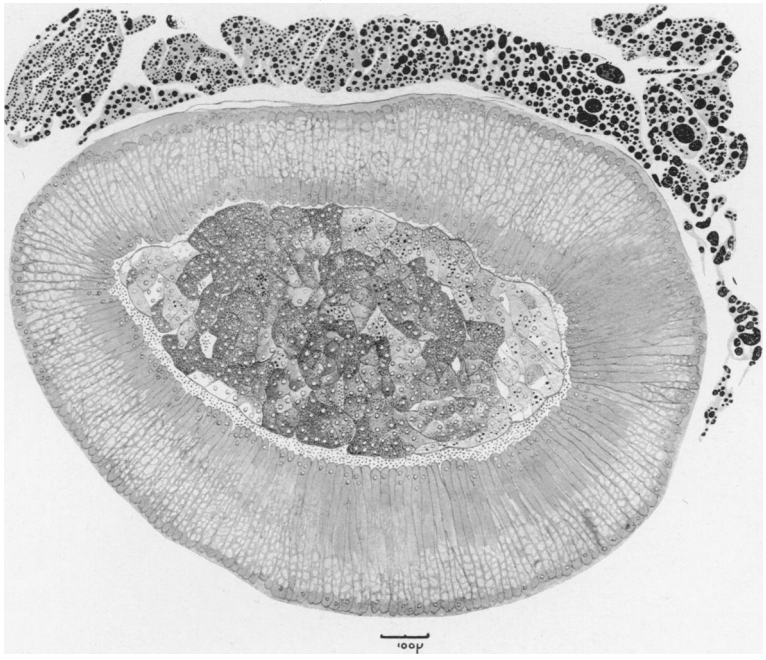

FIG. 1.

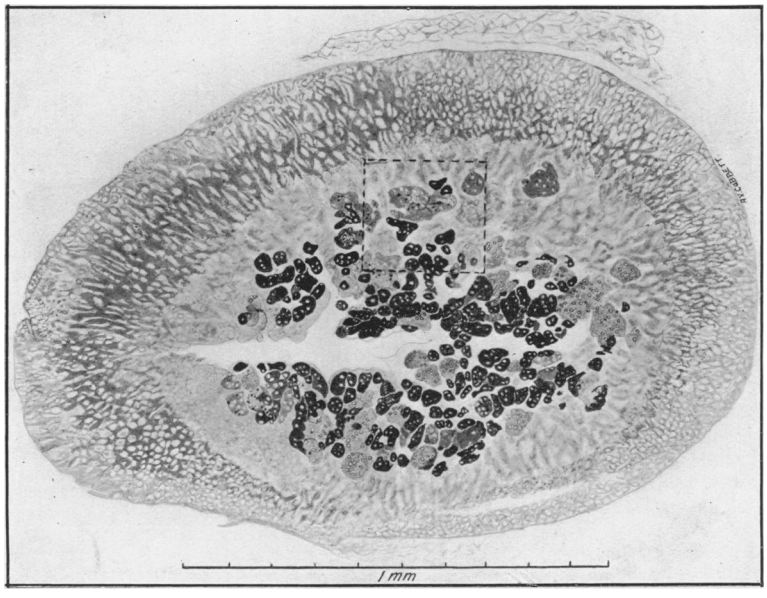

FIG. 2.

Cramer.

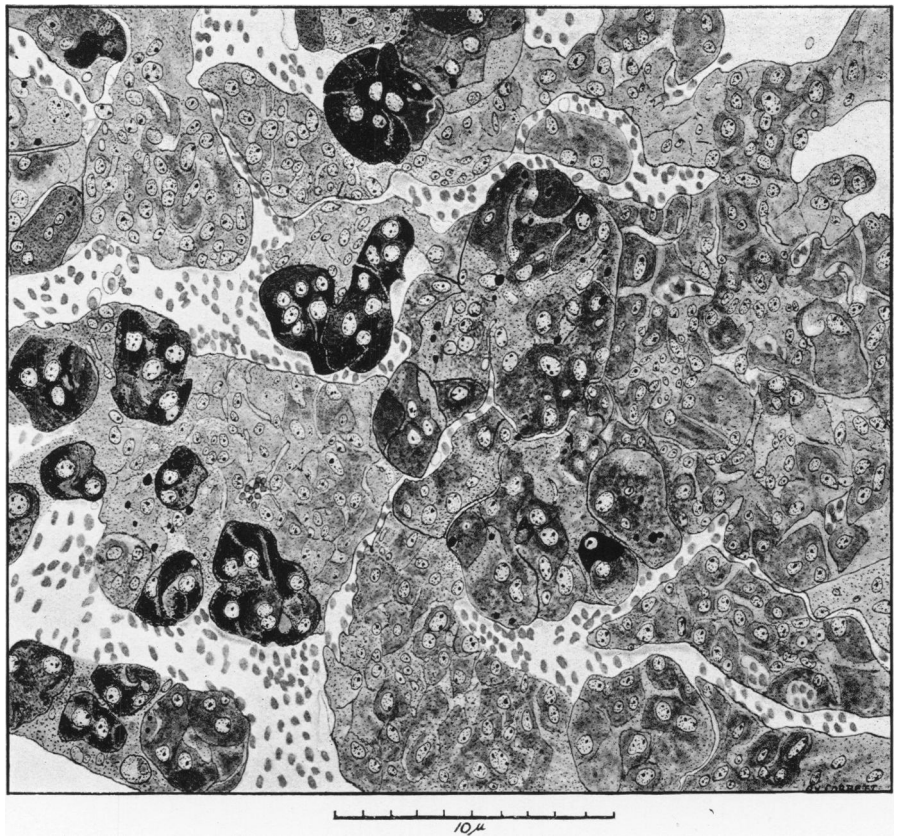

FIG. 3.

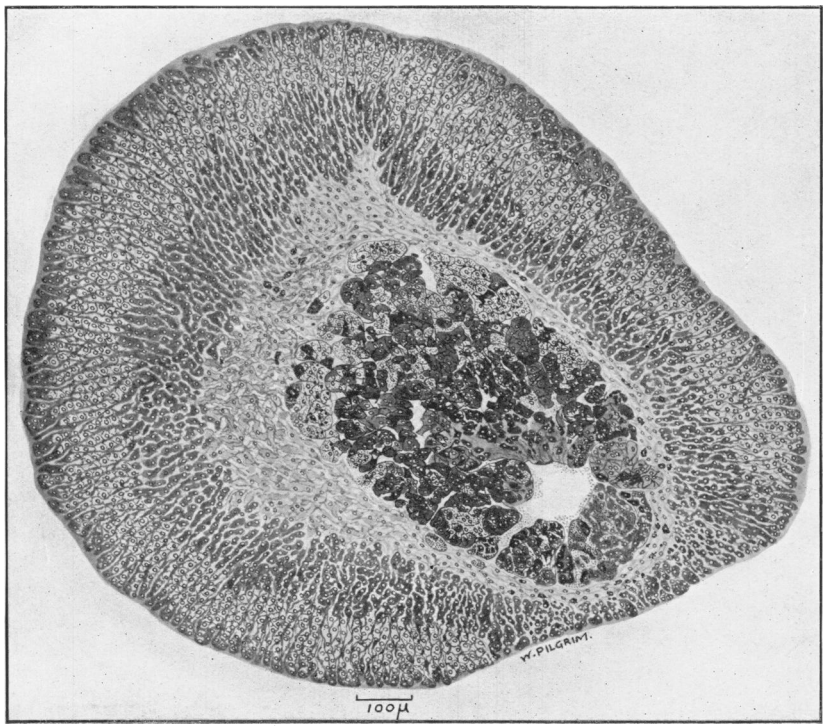

Fig. 4.

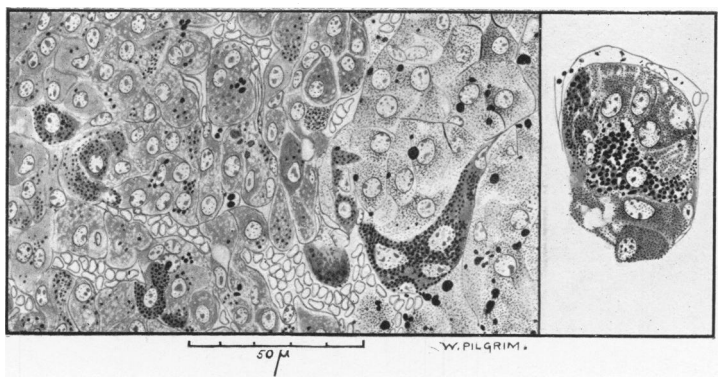

Fig. 6.

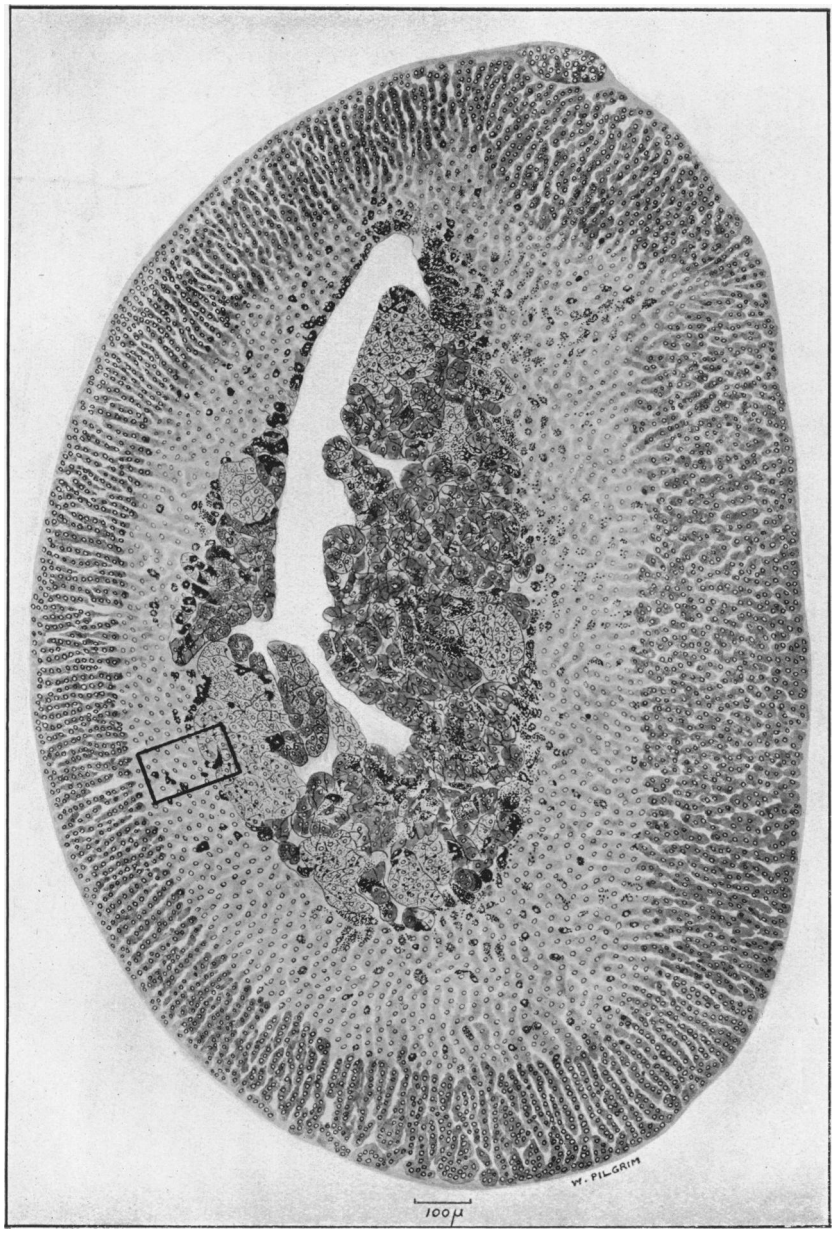

FIG. 5.

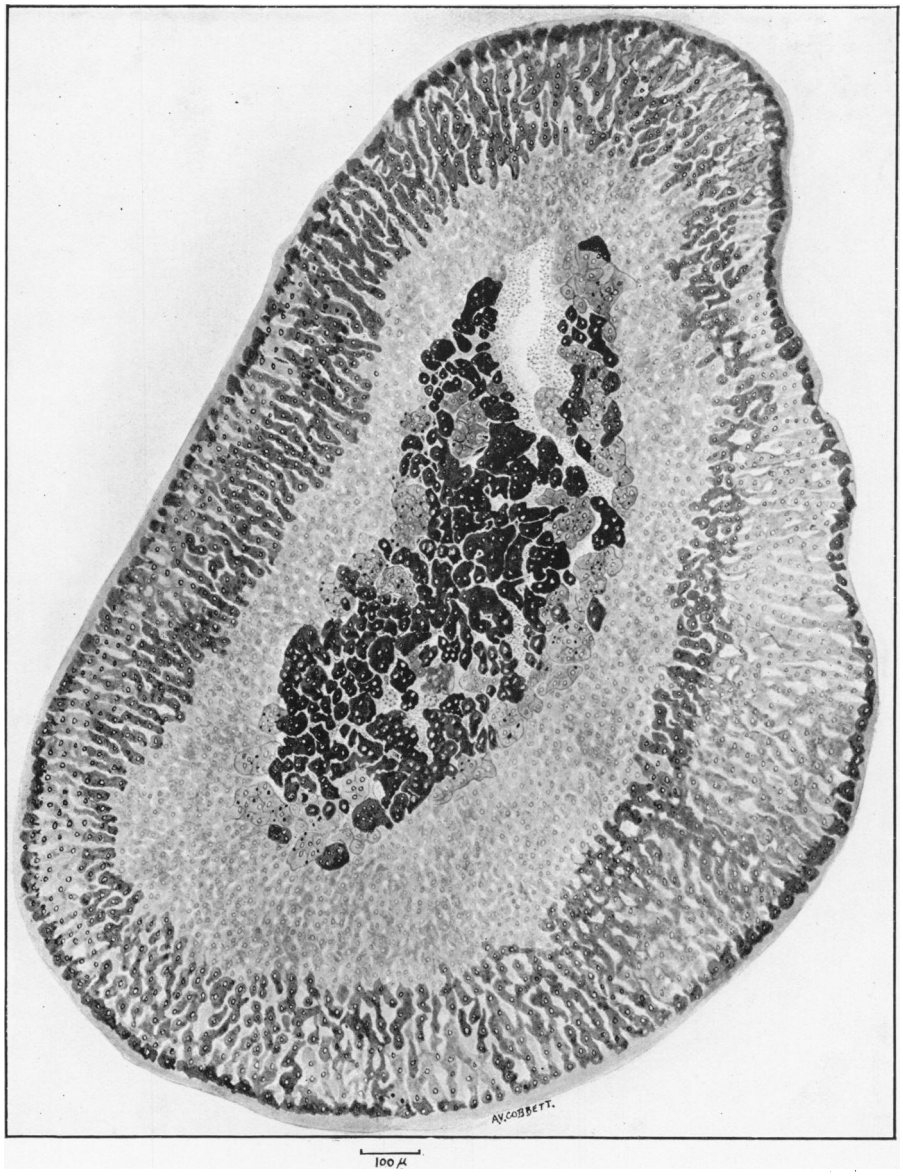

FIG. 7.